PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SAL/PG4814	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/06416	International filing date *(day/month/year)* 18.06.2003	Priority date *(day/month/year)* 20.06.2002
International Patent Classification (IPC) or both national classification and IPC C07C217/58		
Applicant SMITHKLINE BEECHAM CORPORATION ET AL.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.12.2003	27.05.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Rufet, J Telephone No. +49 30 25901-332

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/06416

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-92 as originally filed

Claims, Numbers

1-19 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 18,19

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 18,19 as far as industrial applicability is concerned

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-8 partially, 9 completely and 10-19 partially if applicable .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7,8,10,12-13
	No:	Claims	1-6,9,11,14-19
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 18,19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (article 34(4)(a)(i) PCT).

Re Item IV

Lack of unity of invention

1. This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1 (Claims: 1-8 partially, 9 completely, 10-17 partially)

Provision of compounds of formula (I) according to claim 1 wherein X1 is -CH2- useful for the manufacture of a medicament for treating or preventing dyslipidemia, syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidemia, obesity, anorexia bulimia and anorexia nervosa, which are PPAR mediated diseases or conditions.

Invention 2 (Claims: 1-8, 10-17 all partially)

Provision of compounds of formula (I) according to claim 1 wherein X1 is -SO2- useful for the manufacture of a medicament for treating or preventing dyslipidemia, syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidemia, obesity, anorexia bulimia and anorexia nervosa, which are PPAR mediated diseases or conditions.

Invention 3 (Claims: 1-8, 10-17 all partially)

Provision of compounds of formula (I) according to claim 1 wherein X1 is -CO- useful for the manufacture of a medicament for treating or preventing dyslipidemia, syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidemia, obesity, anorexia bulimia and

anorexia nervosa, which are PPAR mediated diseases or conditions.

2. The International Examination Authority (IEA) fully supports the non-unity objection of the ISA for the same reasons as follows:

According to the description, see especially page 1, first paragraph, the problem underlying the present application is the provision of compounds useful for treating or preventing dyslipidemia, syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidemia, obesity, anorexia bulimia and anorexia nervosa, which are PPAR mediated diseases or conditions.

The proposed solution is the provision of compounds of formula (I) according to claim 1 having as common structural feature the following structure: HOOC-C(R1,R2)-X-Phenyl-X1-N(R5,R6).

Document FR-A-2273518 (D1), see especially p. 1, first paragraph; p. 27, compounds 19, 20 or p. 31, compounds 18, 19 as well as the claims, discloses compounds having the common structural feature. The common structural feature is therefore not new. The compounds of (D1) have an antilipidemic activity (see p. 1, first paragraph) and are therefore useful for treating diseases, like dyslipidemia, hyperlipidemia etc.

It is moreover stressed that the discovery of the mechanism of action of compounds does not render the use of those compounds novel.

The problem underlying the invention can therefore be redefined as the provision of further compounds useful for treating or preventing dyslipidemia, syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidemia, obesity, anorexia bulimia and anorexia nervosa, which are PPAR mediated diseases or conditions.

The 3 inventions mentioned above are different solutions to this problem, which do not share any novel common inventive feature.
Due to the fact compounds having the common structural feature useful for treating or preventing dyslipidemia, syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, type II diabetes mellitus, type I diabetes, insulin resistance,

hyperlipidemia, obesity, anorexia bulimia and anorexia nervosa, are already known from the prior art and due to the fact that no other technical features can be regarded as special technical features in the sense of rule 13.2 PCT, the ISA is of the opinion that there is no single inventive concept underlying the 3 inventions claimed in the present application in the sense of rule 13.1 PCT.

3. Since the Applicants did not pay additional search fees, the examination is only carried out for the invention first mentioned in the claims (invention 1 as abovementioned).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: FR-A-2 273 518
D2: WO 02/28821 A
D3: EP-A-1 067 109
D4: WO 00/23407 A
D5: US-A-3 912 756

1. Novelty:

1.1 Document D1, see especially p. 1, first paragraph; p. 27, compounds 19, 20 or p. 31, compounds 18, 19 as well as the claims discloses compounds falling under the scope of formula (1) of present claims 1-6, 9, 11, 14-17.
The compounds of (D1) have an antilipidemic activity (see p. 1, first paragraph) and are therefore useful for treating diseases, like dyslipidemia, hyperlipidemia etc.
The subject-matter of claims 1-6, 9, 11 and 14-17 is in view of the teaching of D1 not considered to be novel.
It should be noted that the mode of action of compounds is an intrinsic property of the compounds and cannot be a base for a novelty and an inventive step acknowledgement. Moreover the discover of a new mechanism of action cannot make a known use of a known compound novel and also inventive.

1.2 Documents D2-D4 disclose structurally different compounds that activate human peroxisome proliferator activated receptors (hPPAR). The claimed compounds differ from the compounds of D2-D4 by the nature of R5 (D2), X1-NR5R6 (D3), X and X1-NR5R6 (D4) respectively.
Document D5 refers to structurally similar compounds which differ from the claimed compounds of formula (1) by the nature of R6.

2. Claim 1 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved ("hydrolysable ester thereof") which merely amounts to a statement of the underlying problem.

3. Use claim 16 is not acceptable under Art. 6, PCT. The therapeutic application is functionally defined by a mechanism of action which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease).